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Investigating Network-based Proximity in American Biotechnology

Der-Shiuan Lee*

Department of Urban Affairs and Environmental Planning, Chinese Culture University, 55, Hwa-Kang Rd., Taipei 11114, Taipei, Taiwan

Abstract

Proximity among economic agents in spatial clusters fosters invention and innovation. An alternative perspective stresses interregional collaborative networks in which individuals and groups are embedded in wide-ranging webs of relationships. This article use spatial statistical approaches to explore the changing structures of collaborative systems in American biotechnology from 1979 to 2009. Both network and spatial patterns of association on American metropolitan areas over the two periods are explored. Results show that intermetropolitan network complexity has broadened and deepened. While inventors in major metropolitan areas are the foremost collaborators, a dense web of knowledge exchange has emerged that is not singularly controlled by a handful of intermediaries.

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Keywords: Networks; Proximity; Co-invention; Co-patenting; Biotechnology

1. Introduction

Regional differences of inventive activity and economic growth are important issues in economic geography. These differences are generally explained by the theory of *localized knowledge spillovers* (known as LKSs), which argues that geographical proximity of economic actors – inventors, firms, and research institutions – in clusters enhances interpersonal interaction and communication, labor mobility, and research collaboration. Empirical evidence for the presence of LKSs is widespread in cities and regions across the US and Europe. Spatial concentration of inventive firms in clusters enhances the possibility of knowledge exchange and lowers costs

* Corresponding author. Tel.: +886-2-2861-1801 ext. 41121; fax: +886-2-2861-3755.
E-mail address: ldx2@ulive.pccu.edu.tw

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through trade in goods and services, labor mobility, research collaboration, and interpersonal communication [1, 2, 3, 4, 5].

While studies of LKSs and geographical proximity are prominent in the geography of invention and innovation, knowledge flows also occur in wide-ranging circulation, some scholars highlight the role of collaborative networks in which individuals and groups are embedded in webs of social relationships through formal connections and informal linkages [6, 7]. Breschi and Lissoni [8] argued that collaborative networks are channels for knowledge flows that are not limited to local boundaries but can span long distances. This is especially apparent in high-technology industries such as biotechnology where research-collaboration through global networks has become crucial for inventive performance [9, 10, 11]. Combining both local and complementary non-local skills and competences are considered a major strategy for 'firms evolving in a dynamic environment that requires rapid adaptation' [6, p. 1151] and can curtail negative technological lock-in [12, 13]. Phrases such as 'local sticky and global ubiquitous' [12], 'local buzz and global pipelines' [14] stress global and local knowledge exchange within and between different regions. The space of knowledge flows is no longer tightly bundled within a given territorial boundary, but regarded as a kind of network-based system where knowledge flows circulate arounbd alignments of actors in different places [15]. Cities in such a spatially stretched economic sphere are immersed in global networks where knowledge collaboration and exchange are decisive forces for technological advance.

The existence of collaborative networks raises a critical challenge for the investigation and understanding of the complex dynamic and network dimensions of externalities. The focal point here is to investigate the relative importance of spatial compared with network-based proximity on biotechnology co-invention in shaping the US urban structure of knowledge flows. An integrated methodology including both spatial and social network analyses are explicitly applied and compared.

2. Knowledge, proximity, and network-based space

Considerable research effort has been made to identify the nature and strength of LKSs by showing that higher rates of research and development, invention and innovation, entrepreneurial activity, and high-technology production are bounded in space [1, 2, 3, 4, 5]. Other studies increasingly stress that access to external knowledge is also critical to triggering successful innovation and regional development [10, 16]. Breschi and Malerba [17] argued that strong external links vital regional competitive advantages. Bathelt et al. [14] showed that dynamic firms in successful clusters by building and maintaining a variety of internal and external knowledge resources. In addition, advanced information and communication technologies reduce costs of moving knowledge and increase access and availability of universal resources [18]. The concepts of extra-local links and external knowledge resources provide new ways for explaining the geography of invention and innovation. Technological and commercial successes of many firms in Silicon Valley, for example, are closely tied to partners located in other regions and countries [19].

Innovation and invention not only require local interaction between firms within a cluster, but they also need ties among distant actors that provide access to complementary information, skills, and technologies [10, 12, 13]. Knowledge flows are no longer tightly bundled within a given territorial boundary. The relational pattern functions as a network-based system associated with different geographical sites. Knowledge flows in that system are dependent upon shifting alignments of economic actors in different locations in pursuit of particular corporate goals [15]. Many ties between firms in Silicon Valley and Taiwan, for example, are shaped by interpersonal connections between Taiwanese nationals with educational and working experience in both places [19]. A framework of intermetropolitan co-invention networks is proposed here with an emphasis on American biotechnology for the following reasons. First, intense invention and innovation is particularly significant in biotechnology. A large portion of biotechnology value-chains (e.g., venture capital, basic research, R&D, human resources) occurs in few global cities such as Boston and San Francisco in North America, and Cambridge, Munich, and Stockholm in Europe [20]. Second, the global circulation of knowledge through extra-local links provides a diversity of knowledge exchange opportunities for local learning and invention. Individual cities link to and integrate with a global network-based system. Each city has a distinctive knowledge architecture that supports local clients and customers, but they also provide markets and economies of scale for firms whose activities span multiple distant locations [10, 15]. Access to these systems is of particular importance for inventive biotechnology firms located in areas that are remote from the main research and market centers. Successful networking strategies assist in accessing external knowledge. Most remote firms crucially rely on non-local knowledge partners and global networking relationships [21].

I apply social network concepts to figure out intermetropolitan co-invention system of knowledge exchange. Knowledge is embedded in individuals who reside in cities [22]. Figure 1 links the interface between intermetropolitan and social networks and its knowledge circulation. The upper part of the figure shows a simple geographical space with cities A to F, while the lower part is its social network counterpart, as individual inventors are located in different cities. Links in the lower part are co-inventive activities. Some inventors have extra-local relationships with inventors located in other cities, while others only collaborate with local partners. Social relations underpin and facilitate interactions and communication that lead to co-patenting. These inventive-ties shape the intermetropolitan network shown in the upper part of Figure 1. City C is directly connected to A, D, and E, indirectly connected to B, and has no connection with F. Inventors in City F only co-invent with local partners. They are isolated from direct bonds with non-local inventors and it is assumed that they do not exchange knowledge with inventors in other cities.

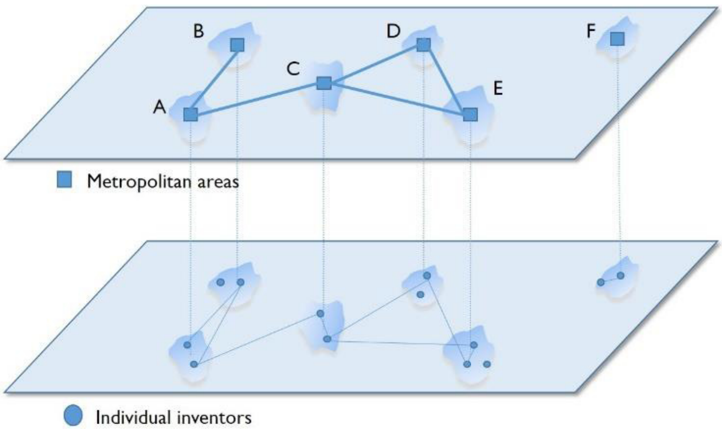


Fig. 1. Intermetropolitan network of co-invention and knowledge circulation.

3. Methodology

Each metropolitan area's co-invention rate (or co-patenting rate, both terms are used interchangeably) is estimated by dividing its annual co-patent count by its total number of wage and salary jobs. The ratio is multiplied by a scaling factor of 1,000. The data for wage and salary jobs were retrieved from the US Bureau of Economic Analysis [23]. The GeoDa 1.6 version for Windows generates the empirical estimates [24].

3.1. Global-level measure of dependence

Moran's I is used to detect global-level spatial and network-based dependencies in biotechnology co-invention across the American metropolitan areas. This statistic provides an overall measure of the strength of cross-sectional autocorrelation in a data distribution [25]. It is calculated by comparing the co-patenting rate of each metropolitan area and the co-patenting rates of its 'spatial' and 'network-based' neighbors. The global-level measure is defined as:

$$I = \frac{m}{\sum_{i=1}^{m}\sum_{j=1}^{m} w_{ij}} \frac{\sum_{i=1}^{m}\sum_{j=1}^{m} w_{ij}(x_i - \bar{x})(x_j - \bar{x})}{\sum_{i=1}^{m}(x_i - \bar{x})^2} \tag{1}$$

where m is the number of metropolitan areas; w_{ij} is an element of an $m \times m$ weights matrix; x_i and x_j are the biotechnology co-patenting rates in areas i and j, respectively; and $\bar{x}$ is the average of all x values. The interpretation of Moran' I statistic is similar to the Pearson's correlation coefficient in that both values range between +1 to -1. When $I > 0$, the overall pattern indicates positive autocorrelation, meaning that areas with similar co-patenting rates, either high or low, are spatially (or network-based) located 'near' each other. When $I < 0$, on the other hand, it shows negative autocorrelation, meaning that areas with dissimilar co-patenting rates are located 'near' each other. When $I = 0$, the overall pattern is random, indicating that metropolitan biotechnology co-invention is independent of either spatial or network-based dependence.

3.2. Local-level measure of dependence

Local analysis is based on a local indicator of spatial association (also called LISA), which allows for the decomposition of Moran's I into the contribution of each individual area. The Local Moran statistic provides a means to assess significance of local spatial patterns [26]. A map combining the information on the locations and the significance of Local Moran statistics is referred to as a LISA cluster map. Ó hUallacháin and Lee's [27] approach is used to distinguish between the following possible local association patterns in both the spatial and network-based systems.

1. Co-invention cores (high-high): These are metropolitan areas with high co-patenting rates and are similar to their neighbors.
2. Co-invention peripheries (low-low): These are metropolitan areas with low co-patenting rates and are similar to their neighbors.
3. High co-invention islands (high-low): These are metropolitan areas with high co-patenting rates but are significantly different from their neighbors.
4. Low co-invention islands (low-high): These are metropolitan areas with low co-patenting rates but are significantly different from their neighbors.
5. Non-significant areas: Based on a conditional permutation approach, these are metropolitan areas with non-significant Local Moran statistics ($p > 0.05$), indicating a failure to reject the null hypothesis of spatial randomness.

Two types of LISA cluster maps, spatial and network-based, are compared to identify significant cores, peripheries, and islands across metropolitan areas. If a co-inventive core (high-high) appears in the spatial LISA cluster map, it indicates that spatial dependence is important in biotechnology co-patenting. If the same neighboring areas constitute a co-inventive core in the network-based LISA cluster map, collaborative relationships are defined by both spatial and network-based associations. More than likely differences in spatial and network-based dependencies occur. In particular, network-based LISA cluster maps with significant no spatial dependence should show co-inventive cores that are geographically scattered. Collaborative networks often favor patenting by inventors living in geographically dispersed locations. Moreover, low co-inventive islands in the network-based system are probably common as few major biotechnology centers exist and most areas' ties are restricted to a few major distant centers.

To capture the neighboring structure of each observation, whether from the aspect of spatial or network-based proximity, needs a weights matrix W specifying the interaction strength between each pair of metropolitan areas.

Each row i of matrix W has elements w_{ij} corresponding to the columns j. Three principal spatial weight choices exist: contiguity (w_{ij} =1 for i and j sharing a common boundary); distance (w_{ij} =1 for $d_{ij} < \delta$) where d_{ij} is the distance between areas i and j; or the number of nearest neighbors. Owing to the 'island' nature of US metropolitan areas and the wide variation in urban spacing, the number of nearest neighbors -- an area's k value -- is perhaps the best spatial choice in identifying neighboring metropolitan areas in the continental US. Concern for the stability of the LISA cluster maps in the Monte Carlo simulations led to the selection of ten nearest neighbors or 7 percent of all possible metropolitan neighbors. This number of nearest neighbors defines discernible regional groupings using the smallest k value.

The network-based weights matrix W_n is based on the annual number of times each pair of metropolitan areas is jointly involved in biotechnology co-patenting. For any two metropolitan areas, an intermetropolitan tie is established if inventors from both areas co-invent the same patent. The more often inventors from distinct areas co-invent, the stronger are intermetropolitan relational ties. This network-based weights matrix W_n is obtained by converting the intermetropolitan network of biotechnology co-invention value matrix into a set of binary relations. The original value matrix is dichotomized using the average number of times that metropolitan areas are tied in biotechnology co-patenting [7]. When the frequency of two areas i and j participating in co-patenting is greater than or equal to an average-based cut-off point then w_{ij} =1, indicating that both areas are relationally connected as neighbors; otherwise w_{ij} = 0. In summary, an intermetropolitan system of biotechnology co-invention is constructed to obtain a network-based weights matrix. The simplest form of an intermetropolitan network consists of a square actor-by-actor matrix, where the rows and the columns represent the same set of metropolitan areas. The relationships between every possible pair of areas provide a way to assess the structure of connections within which these areas are embedded. In this analysis of 150 metropolitan areas, a 150×150 symmetrical matrix was generated for 1979 and 2009. The elements on the off-diagonal are the annual number of times each pair of metropolitan areas joining in biotechnology co-patenting. These elements indicate the nature and strength of interconnected ties that facilitate knowledge flows across urban boundaries.

4. Data and observations

Aspects of biotechnology knowledge exchange are encapsulated in patent co-invention, which occurs when a patent has more than one inventor [28, 29]. I follow Hall et al. [30], Cortright and Mayer [31], and Hevesi and Bleiwas [32] in using US patent classes 424, 435, 514, and 800 to define biotechnology. Classes 424 and 514 are drugs, particularly bio-affecting and body-treating compositions. Class 435 is a chemical grouping and includes molecular biology and microbiology inventions. Class 800 encompasses multicellular living organisms, unmodified parts thereof, and related processes [33]. Patents in these classes in 1979 were extracted from the National Bureau of Economic Research (NBER) databases [30]. The 2009 data were provided by the USPTO [33].

The geographical units in each year are the Metropolitan Statistical Areas (MSAs) defined in the intermediate year of 1999. This common definition identifies 275 areas composed of 258 metropolitan statistical areas and 17 consolidated metropolitan statistical areas (CMSAs). Primary metropolitan statistical areas (PMSAs) are not considered separate cases. Owing to the uneven distribution of biotechnology patents across cities, small areas without any co-patented awards are discarded. This sidesteps swamping the analysis with cases that have no co-patenting and the likelihood that they would be mistakenly identified as outliers. The number of observations is reduced to 150 large areas that had at least one biotechnology co-patent awarded in 1999.

Patents generated by multiple are distinguished from those by solo inventors. Each patent must have at least one inventor located in one of the 150 large metropolitan areas. Foreign partners are ignored, which restricts the analysis to domestic aspects of the American urban system. I specify the geography of biotechnology co-patenting by attributing each co-patent to the metropolitan areas where the inventors reside. Co-patents with inventors living in multiple areas are allocated fractionally, which corresponds with Maggioni et al. [7] and Ejermo and Karlsson [28]. For example, if a co-patent with four co-inventors located in four different MSAs, one-quarter of the co-patent is allotted to each MSA. Some inventors have extra-local relationships with inventors in other areas, while others only collaborate with local partners. The latter are isolated from direct bonds with nonlocal inventors, and it is assumed in this analysis that they do not exchange knowledge with inventors in other areas. The website of US Bureau of Economic Analysis provided the job numbers [23].

Patenting in 351 biotechnology is large and growing—from 883 in 1979 to over 6,356 in 2009, as shown in Table 1. Co-patenting increased faster—from 55 to 81% of biotechnology awards. Average team size increased from 2.54 co-inventors in 1979 to 4.07 in 2009. Table 2 shows the geographical reach of biotechnology co-patenting across the 150 large areas. Most co-patenting occurs within the same metropolitan area, but the trend reveals increasing interconnected collaboration—from 17 in 1979 to 38% in 2009. Moreover, a growing number of metropolitan areas jointly participated in co-patenting, leading to a wider network of collaboration. In 1979, co-patenting never stretched beyond three metropolitan areas, but by 2009, a handful of co-patents tied inventors of five and more areas. In short, knowledge collaboration in biotechnology advance is deepening and broadening across the city system.

Table 1. Number of Biotechnology Patents, 1979 and 2009

	1979	2009
Co-patents	484	5125
Solo patents	399	1231
Total patents	883	6356
Co-patenting percentage*	54.81	80.63

*Co-Patenting Percentage = (co-patents/total patents)×100

Sources: Hall et al. [29], US Patent and Trademark Office [32]

Table 2. Biotechnology co-patenting, percentage intra-metropolitan and intermetropolitan, 1979, 2009

	1979	2009
Intra-metropolitan (co-patenting in the same metropolitan area)	83.2	62.3
Intermetropolitan (co-Patenting with a different metropolitan area)	16.8	37.7
Co-patenting across two areas	16.3	30.0
Co-patenting across three areas	0.5	6.7
Co-patenting across four areas	0.0	0.8
Co-patenting across five Areas (and above)	0.0	0.2

Sources: Hall et al. [29], US Patent and Trademark Office [32]

5. Results

Table 3 shows Moran's *I* results for metropolitan co-patenting rates using the ten nearest neighbors as spatial weights and the co-patenting frequencies as network-based weights, respectively. Only the 2009 network presents significant global dependence with a negative coefficient indicating that metropolitan areas with dissimilar co-patenting rates are significantly network-based associated. This result is interpreted as evidence that biotechnology centers with low co-patenting rates are significantly dependent on ties to a major biotechnology center. This finding for 2009 alone suggests that a set of network-based dependencies are perhaps developing that link minor and major biotechnology centers.

Table 3 Moran's *I* statistics for metropolitan co-patenting rates

(type of weights matrix)	1979	2009
10 nearest neighbors	0.0104 (0.224)	0.0247 (0.141)
Average-based cut-off point = 1	0.0262 (0.131)	
Average-based cut-off point = 2		
Average-based cut-off point = 3		-0.0848 (0.015)

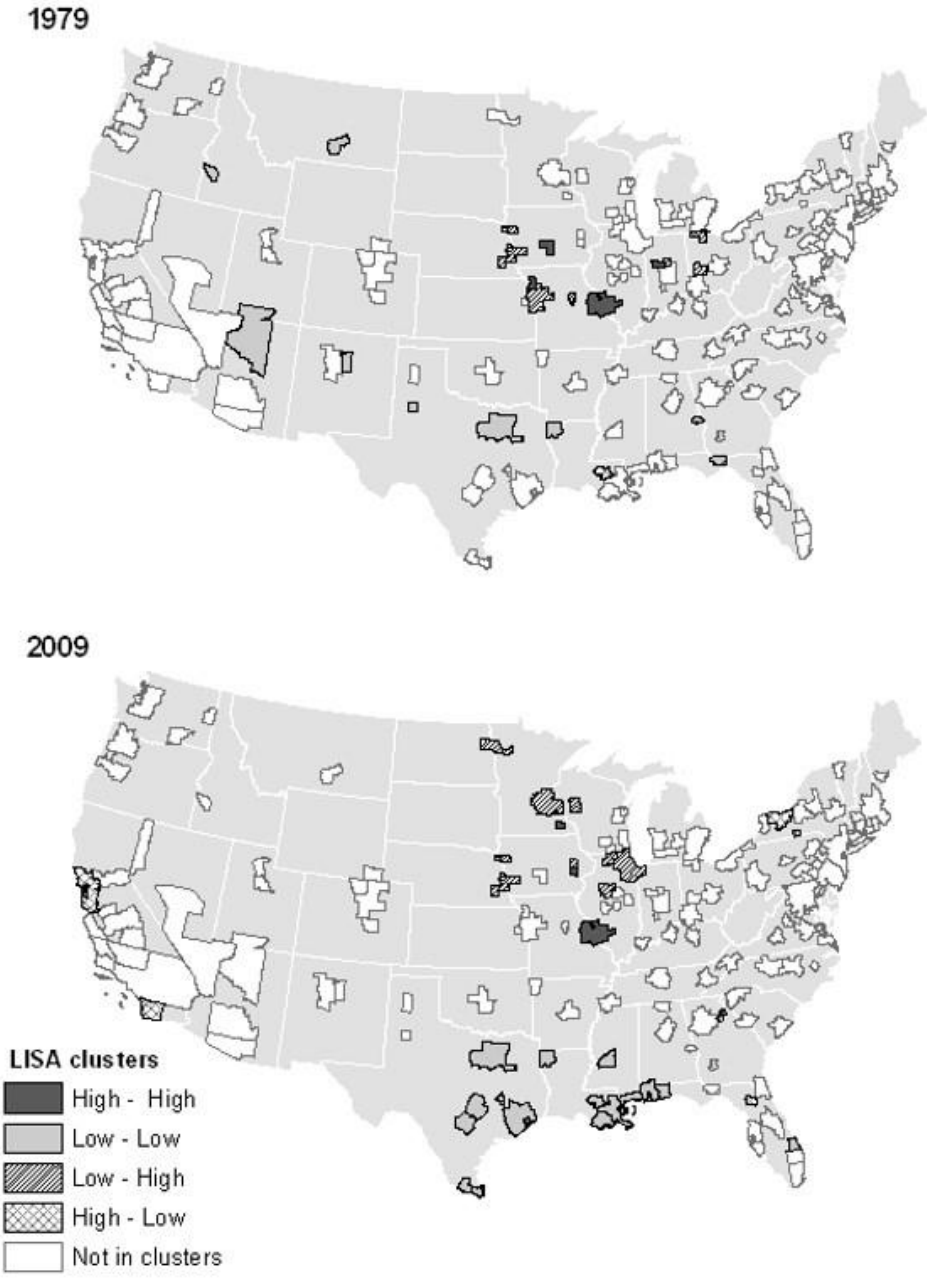
Note: Numbers in parentheses are two-tailed significance levels.

Figure 2 shows spatial LISA cluster maps of metropolitan co-invention using ten nearest neighbors as spatial weights in 1979 and 2009. In 1979, significant LISA clusters are largely absent. A co-invention core of metropolitan areas with high co-patenting rates occurs in the Midwest focused on Lafayette (Indiana), St. Louis (Missouri), St. Joseph (Missouri), and Des Moines (Iowa). This Midwest co-invention biotechnology focus is related to medical research, especially new technologies associated with bacteria. The core has several neighbors that are low co-invention islands. These islands are Sioux City (Iowa), Omaha (Nebraska), Lincoln (Nebraska), Columbia (Missouri), Toledo (Ohio), and Dayton-Springfield (Ohio). An indeterminate co-invention periphery (low-low) occurs throughout the Intermountain West and the Southeast with focal points in Billings (Montana), Boise City (Idaho), Flagstaff (Arizona), Santa Fe (New Mexico), Lubbock (Texas), Dallas (Texas), Shreveport-Bossier (Louisiana), and Tallahassee (Florida). This region is inconsequential in American biotechnology co-patenting. However, in 2009, this co-invention periphery noticeably expanded stretching from east Texas to Alabama. A small co-invention core is evident in the Midwest around St Louis (Missouri), Iowa City (Iowa), and Rochester (Minnesota).

Figure 3 depicts network but not spatial associations of metropolitan areas, which provides an alternative perspective on co-invention ties. The collaborative patterns of American biotechnology based on interconnected co-patenting are mostly composed of low co-invention islands (low-high), and a few prominent co-invention cores (high-high). Over the course of the period 1979-2009, the latter steadily became more explicit and interpretation of the network-based system concentrates on the 2009 results. Major biotechnology centers that form the 2009 network-based core include New York (NY), San Francisco (CA) , Washington-Baltimore (DC), Boston (MA), Denver (CO), Seattle (WA), and Raleigh-Durham (NC). Smaller areas are also focal points of this co-invention core including the university towns of Fort Collins (CO), Iowa City (IA), Lafayette (IN), Lansing (MI), Lexington (KY), Bryan-College Station (TX), and Bloomington-Normal (IL). Santa Fe (NM) with its large national laboratory, Rochester (MN) with a large medical clinic, and New London (CT) that has a cluster of pharmaceutical companies belong to the 2009 core. These areas have high co-patenting rates and their closely network-based associates have high co-patenting rates. These associations suggest that a small number of major biotechnology centers dominate the network-based system. Inventors that co-invent in the minor centers are tied to inventors in the major centers and not to inventors in other minor areas.

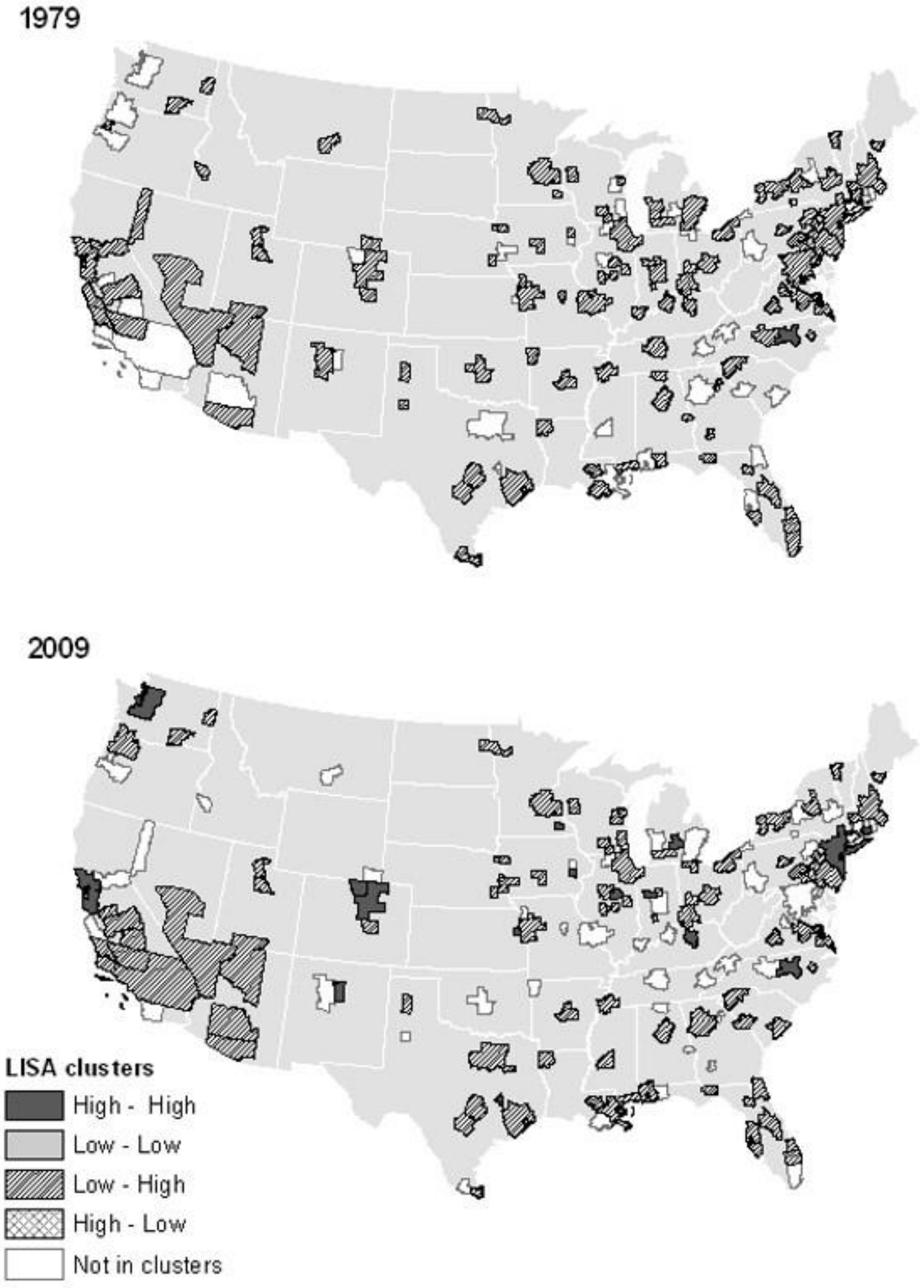
A comparison of the spatial and network-based LISA cluster maps especially in 2009, suggests that the latter better define co-patenting relationships. The 2009 spatial LISA cluster map did not identify any striking spatial associations. A small co-invention core occurs in the Midwest, a periphery is evident from East Texas to Alabama, and San Francisco and San Diego are high co-invention islands. The 2009 network-based LISA cluster map identifies the biotechnology co-invention cores and remaining areas that are far less engaged in co-patenting. However, inspection of co-patenting ties of some of the major co-invention centers show that their network-based associations have regional biases. San Francisco and New York dominate the network-based co-invention core. Their co-invention collaboration spans more than 70 other metropolitan areas across the US. San Francisco's strongest partners are San Diego, Los Angeles, New York, Boston, Philadelphia, and Washington-Baltimore, so its ties are truly national. In contrast, New York's strongest partners are mainly eastern including Boston, New Haven, Hartford, Philadelphia, and Washington-Baltimore. New York is also strongly tied to San Francisco, but its links with Los Angeles and San Diego are weaker. A third example illustrates the role of regional effects. Seattle's collaborations span 40 metropolitan areas but its strongest links are with San Francisco, Los Angeles, and San Diego.

These results suggest that the co-patenting relationships of major biotechnology centers are national and regional but not spatial. Nearest neighbor associations are far less important compared with both network-based and regional relationships.



Note: Nearest neighbor k=10.

Fig. 2. Spatial LISA cluster map of metropolitan co-invention in 1979 and 2009



Note: Average based cut-off point in 1979=1; in 2009=3.

Fig. 3. Network-based LISA cluster map of metropolitan co-invention in 1979 and 2009

6. Conclusions

Co-patenting patterns offer glimpses into networks of collaborative knowledge exchange within and between cities. Theories of localized knowledge spillovers emphasize that geographical concentration of inventive firms, research institutions, and creative individuals. Knowledge transfer is bounded in space because human interaction relies on face-to-face exchange of tacit information. Other scholars stress the role of collaborative networks in which individuals and groups are embedded in wide ranging webs of direct and indirect relationships that span long distances. Corporate technological and commercial success in geographical clusters is embedded in larger network structures where close ties to nonlocal knowledge partners are essential. In order to understand the changing structures of urban collaborative networks, I exploited biotechnology co-patenting datasets that detail key relationships linking US metropolitan areas and compare properties of these systems in 1979 and 2009. Theoretical city systems provide a context for the analysis, and the results are comparable with previous investigations of intercity links.

This research investigates the explanatory roles of spatial and network-based systems in biotechnology information flows. Biotechnology co-invention across 150 American metropolitan areas in 1979 and 2009 is examined. Moran's *I* global test of dependence mostly reveals randomness in both systems. Only the 2009 network-based system turned out to be significant. The coefficient is negative and interpreted as evidence that areas with little co-patenting tend to collaborate with major biotechnology centers. Analysis of local dependence using LISA cluster maps shows few discernable spatial patterns, but the network-based LISA cluster maps highlighted the major co-patenting centers. Minor centers turned out to be significantly dependent on the major centers for invention collaboration. Accordingly, biotechnology co-invention dependence is not spatial, but evidence of some regional effects is noted.

The development of network-based co-invention from 1979 to 2009 reveals that a growing number of urban areas jointly participated in co-patenting as major co-invention centers with significant ties to each other. By 2009, more areas were interconnected and knowledge flows were less likely to be locally bounded and substantial collaboration and exchange occur between distant partners. This result suggests that Cooke's (2006) emphasis on the highest-ranking biotechnology centers overlooks important changes occurring at lower levels. Regional knowledge flows remain robust as New York, for example, has collaborative links with many biotechnology centers across the country, its strongest ties are still on the Eastern Seaboard. In contrast, San Francisco's non-local partners are essential as its co-inventive ties are clearly national in scope, but Los Angeles and San Diego are favored partners. Seattle's ties also span the country, but its co-inventors tend to collaborate more with partners located in the major Pacific Coast centers.

In this article, I tracked co-patenting links in the networks to account for bilateral knowledge flows between metropolitan areas, but the directionality of connections was disregarded. Future research should attempt to distinguish between the incoming and outgoing knowledge flows of each node in the system. I also ignored network connections between American cities. Analysis of global collaboration in biotechnology is clearly needed both to understand the changing properties of the network and the functions of major biotechnology centers. This analysis is extendable to knowledge flows in other technologies. Comparison of biotechnology with, for example, semiconductor, computer, chemical, or mechanical urban systems of technological advance is feasible.

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